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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
04/07/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/579,055	MORI ET AL.	
	Examiner	Art Unit	
	JAMES ANDERSON	1629	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,11 and 16-24* is/are pending in the application.

4a) Of the above claim(s) *1 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 7/15/2010, are acknowledged and entered. Claims 2-5 and 7-10 have been cancelled by Applicant. Claims 21-24 are newly added. Claims 1 and 6 remain withdrawn from consideration. Claims 11 and 16-24 are presently under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/15/2010 has been entered.

Response to Arguments

Applicants' arguments, filed 7/15/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed

invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention.", (see MPEP § 2173).

Claims 11 and 16-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have added the limitation "...wherein the percutaneous absorption type pharmaceutical composition comprises one or more of talc, lactic acid, isopropanol, and polysorbate 80" to claim 11. The Examiner suggests further amending the claim to recite that the percutaneous absorption type pharmaceutical composition further comprises one or more of talc, lactic acid, isopropanol, and polysorbate 80 in order to clearly convey that these are additional excipients added to the formulation recited in the claim. Said "further comprising" language should also be added to claims 21-24.

Claims 11 and 16-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The patient population recited in the instant claims is unclear. The preamble of claim 11 is not so linked to the body of the claim so as to clearly and unequivocally convey that "a patient" is a patient in need of protection against cerebral dysfunction. The Examiner suggests amending claim 11 to recite, "A method of protecting against cerebral dysfunction, comprising administering to a patient in need of protecting against cerebral dysfunction....".

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11 and 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Hiroyoshi et al**. (Japanese Application Publication No. 61-263917) and **Sugita et al**. (USP No. 6,723,732; Issued Apr. 20, 2004; 371 (c)(1), (2), (4) Date: Jul 19, 2001) in view of **Koide et al**. (Japanese Application Publication No. 10-265373), **Akira et al**. (Japanese Application Publication No. 63-203613), **Mori et al**. (EP 0 974 350 A1; Published 1/26/2000), and **Mori et al**. (EP 1 174 132 A1; Published 1/23/2002).

Teachings of Hiroyoshi et al.

As discussed in the previous Office Actions, Hiroyoshi et al. disclose the claimed active agent 3-methyl-1-phenyl-2-pyrazolin-5-one as a cerebral normalizing agent which has cerebral ischemia protecting action (Abstract). Referring now to the English translation of Hiroyoshi et al. provided by Applicants, the inventors disclose the use of 3-methyl-1-phenyl-2-pyrazolin-5-one as an active ingredient for cerebral normalization (page 1 of English translation). Thus, the use of the claimed compound to protect against cerebral dysfunction is not new or unobvious in view of the prior art. As Applicant's correctly observe in their response filed 6/5/2009, Hiroyoshi et al. do not teach percutaneous absorption of the active agent for protecting against cerebral dysfunction.

Teachings of Sugita et al.

Sugita et al. disclose percutaneously administratable preparations containing cerebral function activators (Title; Abstract; col. 2, lines 3-7). In this regard, the inventors teach that orally administrable preparations generally lead to lack of sustained efficacy due to the extreme

rise of blood concentration. The percutaneously administrable preparations of the invention overcome this problem and can reduce individual differences of blood concentration by avoiding the hepatic first-pass effect. Furthermore, percutaneously administrable preparations show continuous pharmacological efficacy because the plasma concentration of the active ingredient can be kept constant for a long duration by the sustained release to whole body circulation (col. 2, line 66 to col. 3, line 11). As such, percutaneous administration of cerebral protecting agents is likewise not new or unobvious in view of the prior art.

The instant claims, as amended, differ from Hiroyoshi et al. and Sugita et al. in that the primary and secondary references do not disclose the claimed excipients of the recited percutaneous absorption type pharmaceutical composition.

Teachings of Koide et al.

Koide et al., as discussed in the previous Office Actions, disclose a tacky adhesive composition comprising a drug, water-soluble polymer, cross-linking agent a polyhydric alcohol and water (Abstract).

The water soluble polymers include rubber polymers such as polyacrylates [0013], and these polymers make up 1-15% [0014].

The formulation comprises crosslinking agents that make up from 0.1-10% of the formulation and include glycine [0017-0019].

The formulation comprises polyhydric alcohols such as ethylene glycol and propylene glycol that make up from 15-50% of the formulation [0020-0021].

The formulation further comprises tackifiers such as cellulosic resins, where the compounds are present in the formulation up to 15% [0020].

The formulations can comprise, as ultraviolet absorption and dispersion agents, **talc** and **titanium dioxide** [0027].

The water content of the formulation ranges from 40-70% [0038]. The drugs range from 0.001-10% of the drug formulation [0031].

The tacky formulation is applied to a film or substrate and applied to the skin [0022]. The tacky topical formulation, while disclosing a wide range of active agents is silent to the specific active agent of the instant claims.

Teachings of Akira et al.

Akira et al. disclose a hydrophilic percutaneous administration preparation containing a percutaneous absorption drug added to a base containing a water-soluble high polymer, a crosslinking agent, and a polyhydric alcohol (Abstract).

Teachings of Mori et al. *('350)*

Mori et al. disclose formulations for percutaneous absorption of tranilast (Abstract). The external preparations are disclosed to be "excellent" in the release of active ingredient, to achieve a high percutaneous absoption, and to fully ensure effective drug concentration in the skin tissue and little irritation to the skin (id.).

The percutaneous absorption composition of Mori et al. comprises an aqueous base containing the active agent, a solubilizer, a dispersant, an absorption aid, an adhesive and/or shape retaining agent, and water (id.; page 3, [0012]).

Mori et al. disclose crotamiton and N-methyl-2-pyrrolidone as recited in claims 16 and 19 as dissolution mediums (page 3, [0016]); 1-menthol, crotamiton, and N-methyl-2-pyrrolidone as absorption aids (page 4, [0025]); tartaric acid as recited in claims 17-18 and 20 as a pH adjuster (page 4, [0026]); and 5 to 15% of water-soluble polymers such as sodium polyacrylate with aluminum hydroxide as a cross-linking agent (page 4, [0028]).

Mori et al. further disclose use of polyhydric alcohols such as glycerol (i.e., glycerin) as adhesives and/or form-keeping agents in amounts of 5 to 40% by weight (page 5, [0030]).

In Example 1 of Mori et al., the inventors teach preparation of a percutaneous absorption preparation that comprises:

i) 0.3% Active agent
ii) 2% Crotamiton
iii) 2.5% N-methyl-2-pyrrolidone
iv) 0.7% White carbon
v) 0.5% 1-menthol
vi) 0.25% Titanium dioxide
vii) 2.5% Tartaric acid
viii) 5% Sodium polyacrylate

ix) 6% Starch acrylate

x) 25% Glycerin

xi) 0.05% Aluminum hydroxide

xii) 52.7% Water

Mori et al. thus teach, suggest, and motivate percutaneous absorption preparations comprising the same excipients as recited in the instant claims.

Teachings of Mori et al. *('132)*

Like Mori et al. ('350), Mori et al. ('132) discloses percutaneous absorption preparations (Abstract).

Mori et al. disclose that the transdermal absorption preparation of the invention may contain "various bases customarily used for the external preparation" as long as they do not affect the other components, such as cross-linking agent, di- or polyhydric alcohols that can be used as the thickening agent and/or the moisturizer, aqueous polymeric compounds, liposoluble polymeric compounds that can be used as the adhesive and/or tackifier, percutaneous absorption accelerators, solvents, surfactants, atablilization agents, and other pharmacologically acceptable additives without limitation (page 4, [0017]).

Suitable cross-linking agents include **aluminum hydroxide** as also disclosed in Mori et al. ('350) and **tartaric acid** and **lactic acid** as rate modifiers (page 4, [0022]).

Polyhydric alcohols include **glycerin** in an amount of preferably 20 to 70% by weight (page 4, [0023]).

Mori et al. disclose that the percutaneous absorption compositions disclosed therein can comprise percutaneous absorption accelerators, including, inter alia, **isopropyl myristic acid** and **isopropanol** (page 5, [0025]).

Preferred solvents for the transdermal absorption preparation of the invention include, inter alia, **water** and **isopropanol** (page 5, [0026]).

Regarding lactic acid as recited in the amended claims, Mori et al. teach that general pH regulating agents can be used as stabilizers including, inter alia, lactic acid (page 5, [0029]).

Regarding polysorbate 80 as recited in the amended claims, Mori et al. teach that examples of surfactants include polyoxyethylene sorbitan monooleic acid (page 6, [0029]).

Regarding talc as recited in the amended claims, Mori et al. teach that examples of inorganic substances include talc (page 6, [0029]).

Mori et al. specifically disclose an aqueous percutaneous absorption preparation prepared by the following steps (page 8, [0040) (disclosed examples of specific agents are indicated in brackets):

i) 0.5% to 5% by weight of active agent is dissolved in 10% to 70% by weight of **water**;

ii) 5% to 25% by weight of N-vinyl acetamide copolymer dispersed in 5% to 20% by weight of **polyhydric alcohol** [e.g., glycerin – page 4, [0023]] in addition to suitable amount of **pH regulating agent** [e.g., lactic acid – page 5, [0029]] is added, then the mixture solution prepared in advance consisting of 20% to 70% by weight of **glycerin** prepared, 0.1% to 10% by weight of **inorganic substances** [e.g., talc – page 6, [0029]] and 5% to 50% by weight of **aqueous polymeric compounds** [e.g., gelatin, sodium polyacrylate, starch acrylate – page 5, [0027]] is added, and stirred;

iii) Subsequently 1% to 15% by weight of a **percutaneous absorption accelerator** [e.g., isopropyl myristic acid and isopropanol – page 5, [0025]] or a **solvent** [e.g., water and isopropanol – page 5, [0026]], or both percutaneous absorption accelerator and solvent, the suitable amount of surfactant [e.g., polysorbate 80 – page 6, [0029]] and pharmacologically acceptable additives are added, and incorporated;

iv) water suspension with 0.1% to 10% by weight of **cross-linking agent** [e.g., aluminum hydroxide – page 4, [0022]] is added and thoroughly kneaded;

v) The aqueous type transdermal absorption preparation of the object is prepared by spreading out the plaster thus obtained over the strippable film and adhering the support to the exposed surface of the plaster opposite to the strippable film side.

Analysis and Examiner's Determination of Obviousness

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use percutaneous administration to administer the cerebral normalizing agent disclosed in Hiroyoshi et al. in light of the obvious benefits of such a mode of administration as disclosed in Sugita et al.

The skilled artisan would expect that any cerebral normalizing agent would benefit from percutaneous administration in light of the teachings of Sugita et al. As such, Applicant's claimed method of administering a known cerebral normalizing agent using a known method of administering such compounds is not patentable over the cited prior art.

It is noted that Sugita et al. disclose formulating active agent in an "aqueous base" as recited in the instant claims (col. 8, lines 59-62) and Koide et al., Akira et al., and the two Mori et al. references all teach, suggest, and motivate aqueous percutaneous absorption compositions comprising the same excipients as recited in the instant claims.

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case, the cited prior art clearly and unequivocally teaches that the claimed excipients are all suitable for incorporation into aqueous based percutaneous absorption preparations. As such, in the absence of factual evidence of an unexpected benefit or property elicited by the specific combinations of excipients recited in the instant claims, administration of 3-methyl-1-phenyl-2-pyrazolin-5-one by percutaneous absorption in an aqueous base with the recited excipients would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants' arguments are moot in view of the new ground of rejection set forth supra. Specifically, Applicants' argument that the applied references do not disclose a percutaneous absorption type pharmaceutical composition comprising talc, lactic acid, isopropanol, or polysorbate 80 is not persuasive because newly cited Mori et al. ('132) discloses percutaneous absorption type pharmaceutical compositions that may contain: i) talc as an inorganic substance; ii) lactic acid as a pH adjusting agent; iii) isopropanol as an absorption accelerator or solvent; and polysorbate 80 as a surfactant.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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